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09/038,609 06/18/99 BOLES

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EXAMINER

EINSMANN, J.

ART UNIT

PAPER NUMBER

1655

10

DATE MAILED:

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.

09/336,609

Applicant(s)

BOLES ET AL.

Examiner

Juliet C. Einsmann

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

## Status

- 1) ☒ Responsive to communication(s) filed on 3/3/00.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) 44-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some \* c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) \_\_\_\_\_.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

## Attachment(s)

- 14) ☒ Notice of References Cited (PTO-892)
- 15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6,9.

- 17) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 18) ☐ Notice of Informal Patent Application (PTO-152)
- 19) ☐ Other: \_\_\_\_\_.

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## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that examination of groups I-II would not place a substantially greater burden on the examiner because applicant argues that the two groups are not distinct and present no search burden. This is not found persuasive for the following reasons:

(a) The instantly claimed groups have obtained separate classifications in the art, indicating that searching the two inventions would require a complete search of two different classes.

(b) Restriction is proper in the case of a product and a method of using if it can be shown that the product can be used in substantially different methods. The reagents in the kit could be used for gene therapy, allele screening methods, anti-sense methods, nucleic acid amplification methods, purification of nucleic acids, in aptamer methods, enzymatic synthesis methods, etc. Each of these represents a distinct method of using the claimed kits, and these have distinct classifications, for example anti-sense probes are classified in 536/24.5 while methods for enzymatic synthesis of nucleic acids are classified in 435/91.2.

The separate classification of groups I and II is *prima facie* evidence that the examination of these inventions would place an undue burden on the examiner. Furthermore, the searches required to examine the instantly claimed methods and the instantly claimed probes would be different, requiring a search of different classes, different electronic databases and the use of different key words in such a search. As such, the restriction requirement is still deemed proper.

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***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-43 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 1-43 are drawn to a method for detecting a non-viral organism in a sample, yet the claims recite a final step of detecting hybridization of a probe. The claims do not set forth the relationship between the detecting hybridization of a probe and the detecting a non-viral organism in a sample and therefore, it is not clear whether the claims are intended to be drawn to a method for detecting a non-viral organism in a sample or a method for detecting hybridization of a probe. Amendment of the claims to read e.g. "wherein the hybridization of the probe is indicative of the presence of said non-viral organism" would obviate this rejection.

Claims 1-43 are indefinite over the recitation of "substantially complementary" because the claims do not provide a clear definition of this term or a method for determining such a level of complementarity. While the specification, at page 9, defines the term "substantially complementary" this definition is not sufficient to clearly provide limitations for this term. Particularly, the specification notes that this term refers to a nucleic acid sequent which will hybridize to the complement of another nucleic acid strand under "stringent conditions" and further the specification notes that one of skill in the art would know how to adjust stringent

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conditions to allow for higher or lower percent mismatch between two nucleic acids. Since the specification lacks a clear definition of the term "substantially complementary" the metes and bounds of these claims cannot be determined.

Claim 22 recites the limitation "the nucleic acid probe" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 20 recites two nucleic acid probes, one in steps (i) and (ii), and another that is gel-immobilized.

Claims 24 and 25 are indefinite because it is unclear which "step of contacting" is meant as base claim 20 has two separate contacting steps.

Claim 27 is indefinite because the additional limitation of the claim conflicts with step (v) of the base claim. Step (v) of claim 20 sets forth the detection of the gel-immobilized probe to the **duplex** SRP RNA, yet claim 27 indicates that both the immobilized probe and the nucleic acid probe comprise sequences which would hybridize to the same region of the sample RNA. It is not possible, then, for the immobilized probe to capture the **duplex**, since the gel-immobilized probe would necessarily have to displace the nucleic acid probe in order for hybridization to occur.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 14, 16, 18, 36, 38, and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention. These claims are drawn to detection methods using the SRP RNA from organisms belonging to specifically listed genera of protozoa, fungi and bacteria. The practice of this invention requires knowledge of the specific sequences of the SRP RNA of these organisms in order to design probes for use in their detection. The specification does not provide specific disclosure of the sequences of SRP RNA for these genera, and further, these sequences would not have been known to one of ordinary skill in the art at the time the invention was made because Zwieb et al. (Nucleic Acids Research, 2000, Vol. 28, No. 1 (171-172)) teach all known SRP RNA sequences and these species are not included in their database. Furthermore and extensive search of commercial databases revealed that these sequences are not disclosed in the prior art. As such, the specification lacks sufficient written description of the claimed invention. With regard to claim 18, the examiner is aware that the SRP RNA sequences for some of the claimed genera are available in the prior art (*Bacillus*, *Pseudomonas*, *Chlamydia*, *Chlostridia*, *Escherichia*, *Helicobacter*, *Legionella*, *Haemophilus*, *Trypanosoma*, and *Ureaplasma*), and these are considered to have met the written description requirement. This rejection applies to claims 16, 18, 38, and 40 with regard to those groups claimed for which there has been no disclosure of the appropriate nucleic acid sequences either in the instant specification or in the prior art.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

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such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-2, 4-8, 10, 12, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Nakamura et al. (Nucleic Acids Research 20(19): 5227-5228).

Hogan et al. teach methods for the identification of non-viral organisms in samples using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T<sub>m</sub>. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T<sub>m</sub> about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions

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will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line 11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Nakamura et al. teach sequence of the SRP RNA (the scRNA) for ten species of *Bacillus*, and further provide an alignment of these sequences (see Fig. 1). Nakamura et al. point out that there is a block containing complete primary sequence identity which corresponds to nucleotides 154-175 of the *B. subtilis* scRNA (p. 5227). Instantly disclosed SEQ ID NO: 2 consists of the reverse complement of nucleotides 154-175 of the *B. subtilis* sequence, and instantly disclosed SEQ ID NO: 3, 4, and 5 are smaller portions of this region.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the SRP RNA taught by Nakamura et al. in the detection method taught by Hogan et al. In light of the combined teachings of Nakamura et al. and the clear teachings on probe selection from as well as the methods taught by Hogan et al. the ordinary practitioner would have been motivated to select a probe from the 21 base pair conserved region of the *Bacillus* genome in order to have created a rapid and effective method for detecting *Bacillus*. One would be motivated to detect *Bacillus* in a sample, and particularly a human sample since it is well known in the art that some species of *Bacillus* are pathogenic to humans, for example *B. cerus*. The combination of the teachings of Hogan et al. with those of Nakamura et al. would have resulted in a rapid and effective method for detecting *Bacillus* in a sample.

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8. Claims 1-2, 4-8, 10-12, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view Griffin (Journal of Biological Chemistry (1975) 250(14):5426-5437).

Hogan et al. teach methods for the identification of non-viral organisms in samples using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T<sub>m</sub>. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T<sub>m</sub> about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line 11)."

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Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Griffin teaches sequence of 4.5 S RNA from *E. coli* (Abstract, Fig. 10) and that the 4.5 S RNA has been shown to be a component of a number of strains of *E. coli*. Instant SEQ ID NO: 6 consists of the reverse complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the reverse complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the reverse complement of nucleotides 65-82. Therefore, the 110 base pair RNA disclosed by Griffin comprises instant SEQ ID NO: 6, 22, and 9.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the 4.5 S RNA taught by Griffin as a probe for the detection of *E. coli* in the methods taught by Hogan et al. in order to have created a method for the detection of *E. coli*. The ordinary practitioner would have been motivated to have used the SRP RNA because Griffin teaches that this RNA has been shown to be a component of a number of strains of *E. coli*. Furthermore, the ordinary practitioner would have been motivated to detect *E. coli* in a sample, including a human sample, because it is well known in the art that some *E. coli* are pathogenic to humans. With regard to the length limitations of claims 6 and 7, the use of any smaller probes would have also been obvious to one of skill in the art, as these would be considered functional homologues of the 100-mer oligonucleotide taught by Griffin since they also would be considered to have the functional property of being able to detect *E. coli*.

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9. Claims 1-2, 4-8, 10-13, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Larsen et al. (Nucleic Acids Research 19(2) 209-215).

Hogan et al. teach methods for the identification of non-viral organisms in samples using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:non-target nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T<sub>m</sub>. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T<sub>m</sub> about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line 11)."

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Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Larsen et al. teach the sequences of SRP RNA from 39 species of organisms, including the 4.5S RNA of *E. coli*. Instant SEQ ID NO: 6 consists of the reverse complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the reverse complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the reverse complement of SEQ ID NO: 65-82. Therefore, the *E. coli* RNA disclosed by Larsen et al. comprises instant SEQ ID NO: 6, 22, and 9. Larsen et al. also teach the SRP RNA sequence from a fungus, specifically, the yeast *Schizosaccharomyces pombe*.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the alignment provided by Larsen et al. and the clear instructions on probe selection provided by Hogan et al. in order to have selected probes useful in the methods taught by Hogan et al. for the detection of any one of the species disclosed by Larsen et al. It would have been further obvious to have used such probes to detect, for example, *E. coli* in humans since *E. coli* is well known in the art to be a pathogen to humans. An ordinary practitioner would have been motivated to develop such a detection assay in order to have provided a rapid method for screening for pathogens in samples. With regard to the length limitations of claims 6 and 7, the use of any smaller probes would have also been obvious to one of skill in the art, as these would be considered functional homologues of the 100-mer oligonucleotide taught by Larsen since they also would be considered to have the functional property of being able to detect *E. coli*.

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10. Claims 1-2, 4-5, 10, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Michaeli et al. (Molecular and Biochemical Parasitology, 51 (1992) 55-64).

Hogan et al. teach methods for the identification of non-viral organisms in samples using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T<sub>m</sub>. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T<sub>m</sub> about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line 11)."

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Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Michaeli et al. teach the sequence of the 7SL SRP RNA of *Trypanosoma brucei*, a unicellular parasitic protozoa (Fig. 3), and teach that 7SL RNA's are divergent at their primary sequence levels among different groups of eukaryotes (p. 56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the SRP RNA of *Trypanosoma brucei* as a probe in the methods taught by Hogan et al. in order to have developed a rapid and effective method for detecting a parasitic protozoan in samples.

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, and 17-19 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, and 17-19 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, and 17-19 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10, and 15-16 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the SRP RNA is labeled.

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Rudert et al. teach that the reverse dot blot technique is useful for detecting nucleic acid sequences, and that in this technique sample nucleic acids are labeled and hybridized to probes bound to a solid support (Col. 3, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a dot-blot technique in the methods taught by reference combinations A-D and thus have labeled the SRP RNA. An ordinary practitioner would have been motivated to use such a technique because Rudert et al. specifically teach that the reverse dot blot technique has advantages which include the ability to screen with many specific probes at the same time simultaneously and in the same container, only one preparation is required to label a large amount of sample nucleic acid and thus, simple and direct comparison of the results between different probes is possible (Col. 3, lines 10-26).

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, and 17-19 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, and 17-19 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, and 17-19 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10, and 15-16 above, and further in view of Rudert et al.

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The teachings of all of the above combinations are applied to this rejection as outlined above. The previously cited references do not teach methods in the nucleic acid probe is a PNA.

Buchardt et al. teach that “peptide nucleic acids (PNAs) are novel DNA mimics in which the sugar-phosphate backbone has been replaced with a backbone based on amino acids (abstract).”

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used PNA probes as taught by Buchardt et al. in the method taught by any one of A-D listed above in order to have provided a more sensitive method for the detection of the SRP RNA since Buchardt et al. teach that PNAs “exhibit sequence-specific binding to DNA and RNA with higher affinities and specificities than unmodified DNA. They are resistant to nuclease and protease attack in serum and cellular extracts and, thus, appear very promising as diagnostic and biomolecular probes (abstract).”

13. Claims 20-22, 24-25, 28-30, 32, 34, and 39-41 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, and 17-19 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Nakamura et al. are applied to this rejection as they are applied above. Hogan et al. in view of Nakamura et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

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Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Nakamura et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected

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results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

14. Claims 20-22, 24-25, 28-30, 32-34, and 39-41 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, and 17-19 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Griffin et al. are applied to this rejection as they are applied above. Hogan et al. in view of Griffin et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic

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carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Griffin et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is *prima facie* obvious in the absence of a secondary consideration such as unexpected results.

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15. Claims 20-22, 24-25, 28-30, 32-35, and 39-41 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, and 17-19 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Larsen et al. are applied to this rejection as they are applied above. Hogan et al. in view of Larsen et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Larsen et al. The ordinary practitioner would have been motivated to include such a step

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in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is *prima facie* obvious in the absence of a secondary consideration such as unexpected results.

16. Claims 20-22, 24-25, 32, and 37-38 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10 and 15-16 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Michaeli et al. are applied to this rejection as they are applied above. Hogan et al. in view of Michaeli et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

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Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Michaeli et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected

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results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

17. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32, 34, and 39-41 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-34, and 39-41 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, and 39-41 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, and 37-38 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the SRP RNA is labeled.

Rudert et al. teach that labeling sample nucleic acid as opposed to probes is advantageous because it simplifies the assay process by allowing the ability to screen samples with many different probes at once (Col. 3, lines 10-26).

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a dot-blot technique in the methods taught by reference combinations A-D and thus have labeled the SRP RNA. An ordinary practitioner would have been motivated to use such a technique because Rudert et al. specifically teach that the reverse dot blot technique has advantages which include the ability to screen with many specific probes at the same time simultaneously and in the same container, only one preparation is required to label a large amount of sample nucleic acid and thus, simple and direct comparison of the results between different probes is possible (Col. 3, lines 10-26).

18. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32, 34, and 39-41 above, and further in view of Urdea et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-34, and 39-41 above, and further in view of Urdea et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, and 39-41 above, and further in view of Urdea et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, and 37-38 above, and further in view of Urdea et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the nucleic acid probe is an adaptor probe comprising a subsequence of that hybridizes to the gel-immobilized probe.

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Urdea et al. teach nucleic acid sandwich assays which utilize an adaptor probe which has regions that hybridize to both the sample and the immobilized probe (Col. 1, lines 50-53).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the probe taught by Urdea et al. in any one of the methods taught by A-D in order to have provided a more efficient capture based detection method since Urdea et al. teach that such a method is advantageous because “using combinations of nucleic acid sequences complementary to a nucleic acid analyte and to arbitrary sequences and specific binding pair members, a detectable label may be separated in two phases in proportion to the amount of analyte present in the sample (Col. 2, lines 29-24).”

19. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32, 34, and 39-41 above, and further in view of Buchardt et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-34, and 39-41 above, and further in view of Buchardt et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, and 39-41 above, and further in view of Buchardt et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, and 37-38 above, and further in view of Buchardt et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. The previously cited references do not teach methods in the nucleic acid probe is a PNA.

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Buchardt et al. teach that “peptide nucleic acids (PNAs) are novel DNA mimics in which the sugar-phosphate backbone has been replaced with a backbone based on amino acids (abstract).”

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used PNA probes as taught by Buchardt et al. in the method taught by any one of A-D listed above in order to have provided a more sensitive method for the detection of the SRP RNA since Buchardt et al. teach that PNAs “exhibit sequence-specific binding to DNA and RNA with higher affinities and specificities than unmodified DNA. They are resistant to nuclease and protease attack in serum and cellular extracts and, thus, appear very promising as diagnostic and biomolecular probes (abstract).”

### ***Conclusion***

20. No claims are allowed.
21. Instant SEQ ID NO: 24 consists of the reverse complement of nucleotides 159-171 of the *P. aeruginosa* 4.5 S RNA as disclosed in Brown et al. (J. Bacteriol. (1989) 171(12) 6517-6520). Therefore, the nucleic acid taught by Brown et al. comprises instant SEQ ID NO: 24.
22. Instantly disclosed SEQ ID NO: 7-11 are free of the prior art. SEQ ID NO: 21, 23, and 16 have not been previously disclosed in SRP RNA.
23. Claims 42 and 43 are free of the prior art.
24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



**JEFFREY FREDMAN**  
**PRIMARY EXAMINER**



Juliet C. Einsmann  
Examiner  
Art Unit 1655

April 24, 2000